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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/704,362	11/01/2000	Kalyanaraman Ramnarayan	24737-1906B	4748
24961	7590	02/04/2004	EXAMINER	
HELLER EHRMAN WHITE & MCAULIFFE LLP 4350 LA JOLLA VILLAGE DRIVE 7TH FLOOR SAN DIEGO, CA 92122-1246			BRUSCA, JOHN S	
			ART UNIT	PAPER NUMBER
			1631	

DATE MAILED: 02/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/704,362	<b>Applicant(s)</b> RAMNARAYAN ET AL.	
	<b>Examiner</b> John S. Brusca	<b>Art Unit</b> 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
  - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
  - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
  - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 03 October 2003.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 23 and 41-53 is/are pending in the application.
- 4a) Of the above claim(s) 43,44,47,48,52 and 53 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 23,41,42,45,46 and 49-51 is/are rejected.
- 7) ☒ Claim(s) 51-53 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 01 November 2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date <u>10/3/2003</u> . | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03 October 2003 has been entered.

### ***Election/Restrictions***

2. In the interview summary mailed 09 December 2003 it was noted that a petition decision concerning a notice of nonresponsive amendment in related Application No 09/709905 (which claims priority to Application No. 09/438566 as does the instant application, and has claims equivalent to a divisional application of the instant application) would control prosecution in the instant application. The petition decision in Application 09/709905 states that because the amended claims continue to read on ab initio methods of structure determination, the amended generic claims are not that of a different invention, but are merely broader than that of the originally filed claims and are therefore a responsive amendment that should be entered. The non-responsive notice mailed 06 November 2003 in the instant application is vacated and the amendment filed 03 October 2003 has been entered into the specification. The petition decision in Application No. 09/709905 goes on to state that if the originally filed claims are determined to be limited to methods requiring an ab initio method of structure determination, the application may be considered to have elected ab initio methods by original presentation. If such is the case, Office policy is to withdraw claims drawn to species other than ab initio methods.

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3. In the amendment filed 03 October 2003, the applicants argue that the originally filed claims were not limited to methods of structure determination requiring ab initio methods because the claims do not recite the term “ab initio” and the specification describes many methods of structure determination.

4. Upon consideration of the applicant’s arguments, it is maintained that the original claims were limited to ab initio methods because of the recitation in all originally filed claims of the phrase “generating 3-D protein structural variant models from the sequences” and “generating a 3-D protein model based on the patient’s gene sequence” in claim 23 because such steps exclude data from sources such as experimental methods or database correlations, and require that the structure is determined ab initio from the sequence data alone. Comments in the notice of nonresponsive amendment mailed 06 November 2003 stating that the phrase “generating a 3-D protein model based on the patient’s gene sequence” were not interpreted to be limited to ab initio methods are withdrawn. Upon further consideration both of the phrases discussed above and the phrase “determining a 3-D protein model based on a patient’s gene sequence” in newly filed claim 50 are interpreted for the purpose of further prosecution to be limited to ab initio methods because the phrases do not explicitly allow for use of information other than that of a gene sequence. The applicant’s amendment filed 03 October 2003 amends the phrase “generating 3-D protein structural variant models from the sequences” in claim 23 to recite “determining 3-dimensional (3-D) protein structural variant models for the proteins that are the product of a gene exhibiting genetic polymorphisms” which is broader because it is not limited to any single method of determining the structure. However amended claim 23 amends the phrase “generating a 3-D protein model based on the patient’s sequence” to recite “determining a

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3-D protein model based on the patient's gene sequence of a protein exhibiting polymorphisms" which continues to be limited to an ab initio method for the reasons discussed above.

5. Claims 42-44, 46-48, and newly filed claims 51 -53 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 42, 46, and 51 are Markush-type claims that read on methods of structure determination other than ab initio methods, namely experimental methods, searching protein structure databases, homology modeling, molecular modeling, de novo protein folding, computational protein structure prediction, and combinations thereof, and will be examined only as they read on ab initio methods as discussed in MPEP 803.02. Claims 43, 44, 47, 48, 52, and 53 are withdrawn as they are drawn to methods of structure determination other than ab initio methods, namely either X-ray crystallography and NMR spectroscopy, or a combination of homology modeling and ab initio methods.

6. Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 43, 44, 47, 48, 52, and 53 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

#### ***Claim Objections***

7. Claims 51-53 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 51-53 are improper because they are not limited to ab initio analysis as is claim 50 from which they depend.

***Claim Rejections - 35 USC § 112***

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23, 41, 42, 45, 46, and 49-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record in the Office action mailed 13 August 2002.

9. Applicant's arguments filed 03 October 2003 have been fully considered but they are not persuasive.

The applicants state that the specification shows how to determine the structure of a protein by use of x-ray crystallography, NMR, or a protein structure database, however the elected invention is limited to ab initio methods.

The applicants point to example 1 in the instant specification however example 1 utilizes prior art crystal structures of the target NS3 protease of HCV rather than the claimed ab initio determination of protein structure.

The applicants point to a number of references in the Information Disclosure Statement filed 13 February 2003. The applicants point to ab initio methods of Belaji et al. (U.S. Patent Nos 5,331,573, 5,579,250, and 5,612,895) as supporting enablement of the elected invention, however Belaji et al. exemplifies ab initio prediction of the structure of endothelin, which is a 21 amino acid peptide, and peptides that bind endothelin. As such, the guidance of Belaji et al. is not commensurate with the scope of the claimed invention which requires ab initio prediction of

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proteins. On pages -37 of the arguments filed 03 October 2003, the applicants appear to argue that the Office has an obligation to prove that the Belaji et al. references could not be used for embodiments of protein structure determination which are beyond the disclosure of Belaji et al. However in order to overcome the rejection of record the applicants burden is to provide prior art references that clearly enable the claimed invention. For reasons of record, the Belaji et al. references do not show ab initio determination of protein structure and do not serve to overcome the rejection of record.

The applicants point to ab initio methods of Osguthorpe. Osguthorpe shows some success at prediction of secondary structure, however Osguthorpe further points out on page 192:

However, these results also show how even with secondary structure predictions of 60-70%, generating correct tertiary structures requires significant additional information as the overall RMS of these structures ranges from 10 to 19 (excluding T0065).

On page 37 of the arguments filed 03 October 2003 the applicants point to one successful result in Osguthorpe. However consideration of the reference as a whole does not show reliable prediction of protein structures by ab initio methods.

The applicants point to Westhead and Thornton for support of enablement, however on page 387 Westhead and Thornton summarize by saying that the quality of models is dependent on comparison to sequences of related sequences with known structures, and that when less than 20% of the sequence of interest is similar to a known structure the modeling algorithms rapidly deteriorate and the inaccuracies are very large. Westhead and Thornton show comparative modeling rather than ab initio structure determination as in the instant claims.

The applicants point to Jones for support of enablement, however Jones summarizes on page 190 that “the predicted structure was quite a long way from the experimental structure.” Jones does not show that ab initio methods are effective.

The applicants point to Samudrala et al. for support of enablement, however Samudrala et al. points out in the abstract that less than half of the proteins analyzed had a predictable structure, and Table 1 shows that the level of resolution of the predictions was low.

Despite the applicants arguments in the response filed 03 October 2003, figure 2 of Sternberg et al. and Table 1 of Koehl et al. show poor performance when no structural data is available.

The applicants further argue that accurate predictions of structure are not required to use the method, however because the method requires prediction of clinical results after comparison of a reference target protein and a variant protein of a patient, it is not clear how such a comparison can be made if the predicted structures are inaccurate.

On page 31 of the applicants response filed 03 October 2003 the applicants argue that Dudek et al. show success using ab initio methods, however Dudek et al. models only short regions of proteins by a combination of ab initio and experimentally determined crystal structures.

On page 31 of the applicants response filed 03 October 2003, the applicants argue that Abagyan et al. shows success with ab initio methods, however analyzed only short peptides of 23 residues or less.

10. The rejection of claims 42 and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which



applicant regards as the invention in the previous Office action mailed 03 April 2003 is withdrawn in view of the positions taken above regarding whether the claims recite ab initio limitations.

*Conclusion*

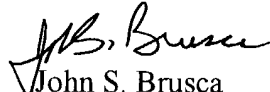
11. All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca whose telephone number is (517) 272-0714. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on (517) 272-0722. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
John S. Brusca  
Primary Examiner  
Art Unit 1631

jsb